REMARKS/ARGUMENTS

Claims 531-576 are pending. Claims 531 and 561have been amended herein. As set forth more fully below, reconsideration and withdrawal of the Examiner's rejections of the claims are respectfully requested.

Examiner Interview

Applicants wish to thank Examiner Desai for the courtesy of a phone interview conducted with Applicants' representatives on 19 August 2005. During the interview, Applicants' representatives and Examiner Desai discussed the remaining rejections under 35 USC § 112 and support in the specification for peptides having only hydrogen atom substituents on the α-amino nitrogen. The Yoshida reference was also discussed including specific discrepancies and suggestions in the data of Yoshida as compared to the teachings of the prior art with respect to the efficacy and mechanism of action of D-penicillimine. These issues are discussed in greater detail below.

Objection to the Claims

The Examiner has objected to Claim 532 as having been mis-identified as a New claim by the status identifier preceding the claim (as opposed to "Previously presented"). The listing of claims presented within this Amendment and Response correctly identifies Claim 532 as Previously presented.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected Claims 561, 562 and 569-576 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner notes that the chemical structures shown and described in Claim 561 are inconsistent with the limitation placed on the α-amino group in Claim 531 that was introduced by the claim amendments filed December 20, 2004.

Applicants have amended both Claims 531 and 561 herein, to remove this inconsistency between the compounds recited in these claims and to more specifically recite the substitutents

on the α-amino group of Xaa_1. Support for these amendments can be found at least in Figure 1 which shows the chemical structures of four metal binding compounds of the present invention having an un-substituted α-amino group and specifically shows compounds of the present invention having an N-terminal amino group bound only to two hydrogen atoms. In light of these amendments, Applicants submit that the chemical structures of Claim 561 are consistent with the compounds claimed in Claim 531, as amended and therefore are sufficiently definite to meet the requirements of 35 U.S.C. § 112, second paragraph.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected Claims 531-576 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner notes that the descriptive phrase "has an unsubstituted α-amino group" is not recited verbatim in the specification. As described above, Applicants have amended Claim 531 to limit the substituents on the α-amino group of Xaa_1 to hydrogen, and support for these amendments can be found in, *e.g.,* Figure 1. In view of this amendment to Claim 531 and the support set forth in Figure 1, Applicants submit that there is adequate enablement in the specification for Claims 531-576, as amended, and request the Examiner's rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claim Rejections Under 35 U.S.C. § 103

The Examiner has rejected Claims 531-576 under 35 U.S.C. § 103(a) as being obvious over Yoshida *et al.*, Neurosurgery 37(2): 287-293 (1995) (hereinafter "Yoshida") in view of Harford and Sarkar, Acc. Chem. Res. 30: 123-130 (1997) (hereinafter "Harford").

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable

expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). There must be a reasonable expectation of success to establish a *prima facie* case of obviousness by modifying or combining references of the prior art (see MPEP § 2143.02). Although obviousness does not require absolute predictability, at least some degree of predictability is required (*Id.*).

The Examiner argues that Harford teaches that peptides having the ACTUN motif effectively chelate copper, and that Yoshida shows that D-penicillamine, a copper chelator, inhibits angiogenesis. Thus, the Examiner argues, it would have been obvious to one of skill in the art to use the copper chelating peptides of the present invention in the treatment of angiogenesis as currently claimed. Applicants respectfully disagree. For the reasons discussed below, Applicants submit that there was not sufficient predictability in the art of inhibiting angiogenesis using metal chelating agents at the time of filing of the application using metal chelating agents to render obvious the presently claimed invention in view of Yoshida.

Yoshida describes an investigation of the effects of a copper depletion diet and the copper chelator D-penicillamine (D-pen) on tumor growth and angiogenesis in a rat gliosarcoma model.

It should first be noted that D-pen is a very different copper chelating molecule than the peptides of the present invention. D-pen is a small 5-carbon molecule with a sulfhydryl side chain [CH_3-$C(CH_3)$SH-$CH(NH_2)$-COOH] that chelates copper ions between two D-pen molecules through a sulfhydryl group from each molecule. Because of these differences in the mechanism of chelation and the size of the molecules, there is no *a priori* reason to expect that the peptide molecules of the present invention would act to chelate copper to the same extent, or with the same kinetics, as the smaller sulfhydryl chelating compound D-pen.

In the Yoshida study, rats were injected subcutaneously with 9L gliosarcoma cells to produce subcutaneous tumors. The animals were divided into two groups (the control group and the group fed a low copper diet and simultaneously treated with D-pen). One animal from each group was sacrificed and the subcutaneous tumor was dissected and examined for the vascular

density of the periphery of the tumor (*i.e.* examined for evidence of angiogenesis). The remainder of the animals were sacrificed and the copper content of the normal brain tissue as well as the copper content of the subcutaneous solid tumor was measured. From this analysis, the researchers showed that the animals fed a low copper diet and treated with D-pen had lower levels of copper in the tumors than in the tumors of the control group animals, however no differences in the copper content of the normal brain tissue between the two groups of animals was seen. The tumor weight of the control group was consistently higher than that of the treated animals over the three weeks following injection of the gliosarcoma cells. Additionally, visual examination of the dissected tumors from one animal from each experimental group showed a lower vascular density and a smaller tumor vessel size in the rat from the D-pen and low copper diet group. From this evidence, the authors conclude that the treatment with D-pen "exerted significant chelating effects on the tumor tissue and decreased the vascular size and the capillary density." (Yoshida, p. 291, col. 1, 1st paragraph).

A. The Study of Yoshida Does Not Conclusively Show the Effectiveness of D-Pen

The conclusions regarding the efficacy of D-pen treatment by the authors of the Yoshida article are clearly too broad to be supported by the research results. For example, there is no evidence presented in Yoshida to demonstrate that the effects on angiogenesis seen in the treatment group were attributable to the D-pen treatment or were not entirely due to the low copper diet. Indeed, the authors of the Yoshida reference point to two earlier studies (Schuschke et al. and Brem et al.) that showed inconsistent results from a Cu depletion diet - one study showing no effect and the other study showing "remarkable hypocupremia with a concomitant smaller tumor volume." (Yoshida, p. 290, col. 2, paragraph 2). From this previous inconsistency, the authors suggest that "inhibition of angiogenesis might require chelation" but then designed and conducted a study that mixes the two variables of low copper diet with copper chelation therapy without taking measures to control for each variable separately. Thus, one of skill in the art would readily recognize that the results of the Yoshida study with respect to angiogenesis

could very well stem from the low copper dietary effects alone. Additionally, there is no indication that the diets of the two study groups described by Yoshida differed only in copper content. Instead the authors only indicate that the diet of the treatment group was low in copper and may therefore have been low in other nutrients, or even simply lower in overall calorie content. It is well known in the art that a reduced calorie diet inhibits tumor growth and the authors of the Yoshida reference make no indication that their results are not due to simple calorie restriction in the study group.

B. Inconsistencies Exist Between the Results of Yoshida and Earlier Published Results and These Inconsistencies Are Not Addressed by Yoshida.

Additionally, the authors of Yoshida do not directly address the inconsistency seen in their data compared to the previously published data by Brem et al. (Yoshida, p. 290, col. 2, paragraph 2). As noted by Yoshida, Brem et al. showed that a low copper diet led to "remarkable hypocupremia" and reduced tumor volume with no change in microvascular density. Yoshida indicates that a low copper diet and D-pen treatment led to decreased microvascular density and tumor volume. Instead of addressing this inconsistency in the data, the Yoshida authors conclude that copper chelation must be responsible for the decreased microvascular density. They reach this conclusion notwithstanding the fact that their data showed no difference in the copper content of the brain tissue from control and treatment group rats and the fact that they did nothing to show that there was any actual chelation of copper by D-pen.

This last point is particularly important as D-pen has been shown to have many cellular and biochemical effects that may be independent of copper chelation. For example, Matsubara et al. (Matsubara, et al., J. Clin. Invest., 83:158-67, 1989, a copy of which is enclosed herewith for the Examiner's review, hereinafter "Matsubara") investigated the effects of D-pen on angiogenesis and showed that the antiagiogenic effects were due to the production of hydrogen peroxide and other reactive oxygen species generated when D-pen was used in conjunction with sufficient quantities of copper sulfate in an *in vitro* and *in vivo* rabbit model. The authors of

Matsubara speculate that the chelation of copper by D-pen results in an interaction that leads to the production of reactive oxygen species that, in turn, exhibit an antiangiogenic effect through inhibition of endothelial cell proliferation. Notably, however, Matsubara shows that the administration of D-pen alone was insufficient to produce the antiangiogenic effect. Thus, D-pen did not reduce angiogenesis unless copper sulfate was administered concurrently - a result that is in direct contradiction to the results of Yoshida. These data raise additional questions about the reliability of the Yoshida data and suggest that the mechanism underlying the beneficial effects of D-pen have not been adequately explained. In reviewing these mechanisms, Matsubara refers to several other cellular effects that have been proposed and tested as the mechanism of action of D-pen in suppressing angiogenesis. For example, D-pen has been implicated to act through intra-articular dissociation of rheumatoid factor (Jaffe, I., J. Lab. Clin. Med. 60:409-421, 1962), aberration of polymorphonuclear function (Chwalinska-Sadowska, H. And Baum, J., J. Clin. Invest. 58:871-79, 1976), effects on collagen crosslinking (Siegel, R.C., J. Biol. Chem. 252:254-59, 1977) superoxide dismutating activity in the presence of copper (Younes, M. and Weser, U., Biochem. Biophys. Res. Commun. 78:1247-53, 1977; and Lengfelder, E. And Elstner, E. F., Hoppe-Seyler's Z. Physiol. Chem. 359:751-57, 1978), inhibition of human helper T cell function in the presence of copper sulfate (Lipsky, P.E. and Ziff, M., J. Clin. Invest. 65:1069-76, 1980) and inhibition of T lymphocyte proliferation (Lipsky, P.E., J. Clin. Invest. 73:53-65, 1984). There is no *a priori* reason to expect that the peptide molecules of the present invention would exert any of the other cellular effects of D-pen noted above.

Therefore, evidence existed at the time of filing of the present invention that suggested that D-pen could work through a myriad of molecular mechanisms and, in some instances, may require the presence of normal to elevated levels of copper to exert an activity. The study described in Yoshida does not address any of these mechanisms nor present any evidence that chelation alone is the mechanism of action of D-pen that led to the effects seen on tumor size and vascularity. Additionally, Yoshida does not directly address the contradiction represented by their results that D-pen, in the absence of significant copper sulfate suppresses angiogenesis in

light of the data of Matsubara that sufficient levels of copper are required for activity of D-pen.

C. Yoshida Suggests that the Kinetics of Copper Chelators Are Important In Determining the Effect on Angiogenesis and This Reseach Must Still be Conducted.

Without directly addressing the study of Schuschke et al. that showed that copper depletion had no effect on angiogenesis nor the study of Matsubara that showed that D-pen alone did not reduce angiogenesis, the authors of Yoshida do allude to the role of kinetics in the effect copper chelators exert on angiogenesis (Yoshida, p. 291, col. 1, 3rd paragraph). The authors explain that copper chelating molecules may act to decrease or to stimulate angiogenesis depending on whether the chelating agent acts to restrict the access of copper to the tumor site or to effectively carry copper in the blood and deliver it to the tumor site. Thus, the authors state that "[m]ore research and complex calculations relating to affinity and transfer kinetics are required to determine whether a carrier molecule becomes a stimulator of cell growth by delivering Cu or whether it becomes an inhibitor of cell growth by removing the bioactivity of the Cu ion." In light of these statements, one of skill in the art would clearly recognize that additional testing and analysis would need to be conducted to determine the effect of any putative antiangiogenesis compound that acted through copper chelation to determine if it had an inhibitory or a stimulatory effect on angiogenesis. Thus, Yoshida itself teaches that the art of inhibiting angiogenesis using metal chelating agents was unpredictable.

D. At Best, Yoshida Provides an Impetus to Try Other Chelating Compounds in Suppressing Angiogenesis.

Applicants submit that obviousness cannot be established in the face of such unpredictability in the art-specific literature that would leave the skilled artisan without a reasonable expectation of success in suppressing angiogenesis by copper chelation. At best, the data presented in the Yoshida reference amount to an assertion that one of ordinary skill in the relevant art would have been able to arrive at Applicants' invention because it would have been

"obvious to try" substituting other chelating agents, and selecting entirely different dosing and kinetic characteristics, in order to produce the claimed invention. The Federal Circuit has provided clear direction with respect to arguments based on an "obvious to try" theory. The court has held that an "obvious to try" situation exists when a general disclosure may pique a scientist's curiosity, such that further investigation might be done as the result of a disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued. In re Eli Lilly & Co., 14 USPQ 2d 1741, 1743 (Fed.Cir. 1990). The court held, however, that "obvious to try" is not to be equated with obviousness under 35 U.S.C. §103. See Gillette Co. v. S.C. Johnson & Son, Inc., 16 USPQ 2d 1923, 1928 (Fed.Cir. 1990). For the foregoing reasons, Applicants respectfully submit that because neither Yoshida nor Harford, alone or in combination, provide sufficient evidence to predict the success of any copper chelator or the specific peptide chelators of the present invention in suppressing angiogenesis to direct one of ordinary skill in the art to make the present invention, the Examiner should withdraw all §103 rejections predicated upon this combination.

Based upon the foregoing, Applicants believe that all pending claims are in condition for allowance and such disposition is respectfully requested. In the event that a telephone conversation would further prosecution and/or expedite allowance, the Examiner is invited to contact the undersigned.

Respectfully submitted,
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Date: 7 Sept. 2005